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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,174	09/19/2001	William G. Kerr	USF-T150CX	9411

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,174	KERR, WILLIAM G.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2005 and 15 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2-9-05, 4-4-05, 3-15-05, 2-6,03*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communications filed 2-9-05 and 2-15-05.

Claims 38-87 are pending in the instant application.

The declaration under 37 CFR 1.132 filed 2-9-05 is insufficient to overcome the rejection of claims 38-87 based upon 112, first paragraph as set forth in the last Office action for the reasons set forth below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-9-05 has been entered.

Sequence Compliance

The CRF filed on 2-9-05 has been entered. The RNAi sequences disclosed in Dr Kerr's declaration (and which sequences are now submitted in the CRF) were not provided in the original disclosure at time of filing and therefore would constitute new

matter. Please provide support for these submitted sequences in the originally filed application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections and Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-87 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods comprising an RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells, or comprising a nucleic acid molecule that hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA or hybridizes in vivo with SHIP-1 mRNA present in mouse or

human hematopoietic cells. The specification and claims do not adequately describe the broad genera comprising either *an RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells* or *a nucleic acid molecule that hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA or hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells*. These genera encompass a broad array of nucleic acid molecules, and the disclosure fails to provide a representative number of species for either of the broad genera claimed. The specification and claims do not adequately describe the concise structural features (e.g. the nucleotide sequences) that distinguish structures within each genus from those without. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe these very broad genera claimed. Thus, Applicant was not in possession of the claimed genera, comprising either an RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells or comprising any nucleic acid molecule (and of any size) that hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA or hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells.

Applicants' arguments and declaration filed 2-9-05 have been fully considered but they are not persuasive. Applicants argue that since human and mouse isoforms of SHIP-1 have been identified, and in addition, since rat and a potential chimpanzee homologue have also been reported, adequate written description has been provided for these broad genera claimed. Contrary to Applicants' assertions, the characterization of the various isoforms of SHIP-1 in mouse and human, along with the identification of a

rat homologue and a potential chimpanzee homologue, do not provide for adequate written description of the genera comprising any RNAi or any nucleic acid that specifically hybridizes with SHIP-1 mRNA present in human or mouse hematopoietic cells. Applicants also argue that a list of every possible permutation of nucleic acid sequences should not be required for sufficiently or adequately describing the genera claimed. Applicants are correct that such an exhaustive list need not be provided to fulfill written description requirement. On the other hand, a representative number of species is required for such broad genera. The genera include sequence variations that can range between 70 and 100% with the intended target sequences of mouse or humans, and include sequences of an unspecified size range. The identification of SHIP-1 in other species does not provide the requisite guidance for adequately describing the array of molecules claimed. For these reasons, the written description rejection is maintained.

Claims 38-87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of suppressing the rejection of an allogeneic bone marrow graft from BALB/C mice in SHIP-/- mice or abrogating GVHD disease in SHIP-/- mice that were transplanted with whole bone marrow from BALB/C mice, thereby enhancing SHIP-/- mice survival, and while being enabling for the in vivo inhibition of SHIP-1 expression in mice using the RNAi sequences #1, #4 and the mouse antisense vector muSHIPshRNA provided in the declarations by Dr. Kerr, filed 7-21-04 and 2-9-05, does not reasonably provide enablement for inhibiting SHIP-1 in vivo

comprising the administration of *any* RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells, or comprising the administration of *any* nucleic acid molecule that hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA or that hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells, nor of preventing a transplant rejection in any patient, or preventing or treating graft versus host disease (GVHD) in any patient comprising the administration of any interfering RNA specific for SHIP mRNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods for inhibiting SHIP-1 in vivo, for suppressing or preventing a transplant rejection in a patient, and for preventing or treating graft versus host disease (GVHD) in a patient comprising the administration of an RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells, or comprising a nucleic acid molecule that hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA or hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells, whereby SHIP-1 expression is inhibited in that organism and treatment effects provided.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of nucleic acid treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo inhibition of target genes. (A. Branch, Trends in Biochem. Sci. 23: 45-50, document "BA" in IDS filed 11-17-03, *see* entire text for Branch; S. Crooke, Antisense Res. and Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using oligonucleotide based approaches Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate... cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol., 14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: AIt is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide

(S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of ... oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the Aimportant and inordinately difficult challenges of the delivery of therapeutic oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting the expression of SHIP-1 in vivo comprising the administration of any RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells, or comprising the administration of any nucleic acid molecule that hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA or that hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells. Applicants have not provided guidance toward a method of treating or preventing a transplant rejection in a patient, or preventing or treating graft versus host disease (GVHD) in a patient comprising the administration of an interfering RNA specific for SHIP mRNA. The specification teaches the suppression of the rejection of a an allogeneic bone marrow graft from BALB/C mice in SHIP-/- mice, as well as the abrogation of GVHD disease in SHIP-/- mice that were transplanted with whole bone marrow from BALB/C mice, whereby SHIP-/- mice survival was enhanced. The

declarations filed 7-21-04 and 2-9-05 teach the in vivo inhibition of SHIP-1 following the co-administration of RNAi sequences #1, #4, or following the administration of the mouse antisense vector muSHIPshRNA.

The ability of these co-administered RNAi's, or of the mouse antisense vector muSHIPshRNA to target and successfully inhibit expression of the target gene encoding SHIP1 in a mouse model, and provide for an observed increase in Mac+Gr1 monocytes and circulating Mac1+GR1+cells (myeloid suppressor cells) is not representative of providing other treatment effects including altering NK function, preventing transplant rejection in any patient, or preventing or treating graft versus host disease (GVHD) in any mammal following administration of RNAi, or following administration of the mouse antisense vector muSHIPshRNA. Nor is it representative or correlative of the ability to achieve in vivo SHIP-1 inhibition of expression or treatment effects comprising the administration of any RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells or comprising any nucleic acid molecule (and of any size) that hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA or hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells.

In addition, one skilled in the art would not accept on its face the examples given in the specification of the enhanced survival and reduction of transplant rejection in a mouse model using SHIP-/- mice as being correlative or representative of the successful inhibition of expression of SHIP in vivo using interfering RNA specific for SHIP mRNA, and further whereby treatment or prophylactic effects are provided for

transplant rejection or graft versus host disease (GVHD) in a patient in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the efficacy of interfering RNA in inhibiting the expression of SHIP in any organism and in treating, suppression or preventing transplant rejection or graft versus host disease (GVHD) in a patient following administration by any route of the claimed oligoncucleotides. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and treatment effects provided by the claimed oligonucleotides administered, and specifically regarding the instant compositions and methods claimed.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to compositions and methods for inhibiting SHIP-1 expression in vivo, and for suppressing or preventing a transplant rejection in a patient, or preventing or treating graft versus host disease (GVHD) in a patient comprising the administration of an interfering RNA specific for any SHIP mRNA, whereby SHIP expression is inhibited in that organism comprising the administration of any RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells or comprising any nucleic acid molecule (and of any size) that hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA or hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery

and formulations to target appropriate cells and /or tissues harboring the target gene or genes SHIP-1, whereby SHIP expression is inhibited in vivo, and further whereby treatment and/or prophylactic effects are provided for transplant rejection or graft versus host disease (GVHD) in a patient comprising the administration by any means of any RNAi of any size specific for SHIP-1 mRNA present in human or mouse hematopoietic cells or comprising any nucleic acid molecule of any size that hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA or hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells. Since the specification fails to provide any particular guidance for the successful targeting and inhibition of expression of SHIP-1 in vivo comprising administration of any nucleic acids encompassed by the broad genera claimed, or for the successful treatment, suppression or prevention of any transplant rejection or graft versus host disease (GVHD) in an organism following administration of any nucleic acid encompassed by the broad genera claimed, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Applicants' arguments and declaration filed 2-9-05 have been fully considered but they are not persuasive. Applicants argue that the SHIP1 ablation experiments provide for such phenotypes as altered NK cell function and GVHD, and that there is no reason to doubt that reduction of SHIP1 function by RNAi or other means of SHIP1 inhibition will be of therapeutic benefit in suppressing transplant rejection and GVHD in mammals. Contrary to Applicant's assertions, the success of two RNAi's in their ability

to target and successfully inhibit expression of the target gene encoding SHIP1 in a mouse model, and provide for an observed increase in Mac+Gr1 monocytes and circulating Mac1+GR1+cells (myeloid suppressor cells) is not representative of obtaining in vivo SHIP-1 inhibition of expression comprising the administration of *any* RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells, or comprising the administration of *any* nucleic acid molecule that hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA or that hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells, nor of preventing a transplant rejection in any patient, or preventing or treating graft versus host disease (GVHD) in any patient comprising the administration of any interfering RNA specific for SHIP mRNA. The unpredictability lies not in the ability to completely ablate SHIP-1 expression and provide for treatment effects, but instead to successfully deliver adequate dosage of the inhibitory (RNAi) molecules claimed whereby the therapeutic effects claimed are obtained.

The animal models provided in C. elegans, zebrafish, Drosophila and mammalian cell culture (as taught previously by Zamore et al and Svoboda et al, cited on p. 2 of Dr. Kerr's declaration filed 7-21-04) using RNAi provide particular guidance resolving issues associated with in vivo delivery of oligonucleotides and treatment effects. Contrary to Applicant's assertions, the examples provided pertaining to RNAi in systems such as C. elegans, zebrafish and Drosophila are not representative or correlative of the ability to target appropriate target cells harboring SHIP1 mRNA in a mammal. The in vivo systems of these lower organisms are significantly different from

mammals, and, while the RNAi results provided in these systems are encouraging for studying the roles of particular target genes thought to be related or analogous in higher organisms, they are not predictive of successful in vivo targeting and inhibition, and further whereby treatment effects are provided in a mammal. In addition, the in vitro targeting and inhibition of the same target gene (SHIP1) in mammalian cell culture (including ES cells as described on p. 3 of Dr. Kerr's declaration, filed 7-21-04) are not representative of in vivo targeting and inhibiting any mammalian SHIP1 in an organiam. In vitro results cannot be extrapolated to in vivo gene inhibition and subsequent treatment effects. In vivo results require undue experimentation, and cannot be generalized from a test tube (or cell culture) to an organism.

Applicant argues that the instant specification reviews existing gene delivery vehicles that can be used to deliver nucleic acids that target and reduce SHIP function according to the subject invention. Contrary to Applicant's assertions, a review of existing gene delivery vehicles for performing experiments in the future is not enabling for the full scope claimed. It is noted that Applicant will not have to reinvent the wheel in order to discover new gene delivery devices, and many are available and well known in the art. It is also noted that those already employed successfully by Applicant (e.g. using the RNAi molecules labeled #1 and #4, and the antisense vector used to inhibit mouse SHIP1 in vivo as described in the declaration filed 7-21-04) are enabled, but these are not representative of the broad scope claimed.

Applicant also argues that the in vivo results obtained in mice using the RNAi sequences #1, #4 and the mouse antisense vector muSHIPshRNA provided in the

declarations by Dr. Kerr, filed 7-21-04 and 2-9-05 are representative and correlative of the ability to successfully target and inhibit expression of any mammalian SHIP1 mRNA in an organism and provide treatment effects such as altering NK function in a mammal, preventing a transplant rejection in any patient, and preventing or treating graft versus host disease (GVHD) in any patient comprising the administration of an interfering RNA. Contrary to Applicant's assertions, the success of two RNAi's in their ability to target and successfully inhibit expression of the target gene encoding SHIP1 in a mouse model, and provide for an observed increase in Mac+Gr1 monocytes and circulating Mac1+GR1+cells (myeloid suppressor cells) is not representative of providing other treatment effects including altering NK function, preventing transplant rejection in any patient, or preventing or treating graft versus host disease (GVHD) in any mammal. Nor are these two RNAi's representative of the ability of the broad genera of nucleic acid molecules claimed to provide for the same treatment effects, or provide for in vivo target gene inhibition. The ability to obtain the extent of target gene inhibition (in appropriate target cells in a particular organism) using a particular RNAi for obtaining these various treatment effects requires undue experimentation beyond that taught in the instant disclosure, and cannot be substituted with the other phenotype obtained (i.e. myeloid suppressor cell increase). Applicant argues that because the SHIP1 ablation experiments provide for such phenotypes as altered NK cell function and GVHD, there is no reason to doubt that reduction of SHIP1 function by RNAi or other means of SHIP1 inhibition will be of therapeutic benefit in suppressing transplant rejection and GVHD in mammals. Applicants are correct that the ablation experiments show promise for the

therapeutic capability of RNAi and similar inhibitory approaches. But, in order for the full scope of the instant invention to be enabled, the results obtained using ablation experiments cannot be substituted for the unpredictable endeavor of providing treatment effects including altering NK cell function and GVHD in any mammal using any RNAi targeting any mammalian SHIP1 mRNA. It is still highly unpredictable that complete ablation will be obtained using these inhibitory molecules, and a measure of the extent of target gene inhibition required to achieve this treatment effect (observed in an ablated mouse model) must be determined empirically and therefore requires undue experimentation. Therefore, the instant rejection for lacking enablement over the broad scope claimed is maintained.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ɜ 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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